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Original Research

Determination of Bisphenol A and 4-Nonylphenol in Water Using Ionic Liquid Dispersive Liquid Phase Microextraction

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Abstract

A response surface optimization based on ionic liquid dispersive liquid phase microextraction was developed for analysis of the endocrine disrupting compounds bisphenol A and 4-nonylphenol in water samples. The volume of the extraction solvent, volume of dispersive solvent, and pH were found to have significant effects on the response. Analysis of variance indicated that the model was significant at a high level. The reproducibility was investigated in six replicate experiments under optimum conditions. Taken together, these results indicated that the developed method would be a useful green method for rapid determination of bisphenol A and 4-nonylphenol at trace levels in tap and surface waters.

Keywords: dispersive liquid phase microextraction, endocrine disrupting compounds, ionic liquid, response surface method, water

Introduction

Pollution of aquatic systems caused by endocrine disrupting compounds (EDCs) at drinking water treatment plants has become an important international topic. There is increasing evidence of the risks associated with these compounds because of their effects as endocrine disruptors, which change the function of natural hormones in the body and tend to be persistent in the environment [1-3]. Among phenolic EDCs, increasing attention has been focused on the health risks of bisphenol A (BPA) and 4-nonylphenol (4-NP) owing to their high production, widespread use, and ubiquitous occurrence in the environment [2, 4]. For this reason, it is necessary to get a clearer picture of BPA and 4-NP levels in water samples, especially in drinking water.

Recently, many analytical techniques such as ultrasonic extraction [5], solid phase extraction (SPE) [1, 2, 6], and solid phase microextraction (SPME) [7] have been developed for the extraction of EDCs in aqueous samples. However, except for SPME being expensive, these other conventional methods are tedious, time-consuming, and require large amounts of solvents. A new and novel technique, dispersive liquid phase microextraction (DLPME) [8], is gaining popularity because it is simple, rapid, and economical. With the obvious advantages of high recovery and enrichment factors, simplicity, rapidity, and low cost, this method has been used for determination of amide herbicides [9], pesticides[10-12], Polycyclic aromatic hydrocarbon (PAHs) [13, 14], carbamates [15], emerging contaminants [16], trace metals [17-19], aromatic compounds [20], triclocarban (TCC), triclosan (TCS), [21] etc. Although DLPME has many merits, toxic solvents such as chlorobenzene, chloroform, or carbon tetrachloride are used for the extraction; accordingly, environmentally friendly solvents are needed. Ionic liquid is an interesting green solvent that can reduce the effects of toxic organic solvents on the environment. Owing to its good

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extraction efficiency for the separation of abundant inorganic and organic compounds, ionic liquid is widely used in liquid-liquid extraction [22] and liquid membrane extraction [23]. López-Darias et al. [8] compared the application of two liquid-phase microextractions, single-drop microextraction, and DLPME for determination of several endocrine-disrupting phenols in seawater. Zhao et al. [21] developed a dispersive liquid-liquid microextraction with ionic liquids for enrichment and determination of TCC and TCS. In the ionic liquid dispersive liquid phase microextraction (IL-DLPME), the ionic liquid was dispersed completely into the aqueous phase, which increases the chance of mass transfer into the ionic liquid phase. The ionic liquid was then concentrated into one drop by centrifugate.

Classically, the test is optimized by altering one variable at a time, but this cannot yield optimal conditions for the interaction of multiple variables [24]. Consequently, the response surface method (RSM) was selected to evaluate the relative significance of variables and determine the optimal conditions for the related response. Over the past several years, the RSM has been applied for optimization of analytical conditions in methods such as solid phase extraction [25], micellar electrokinetic chromatography, [26] fluorometry, [27] and flow injection analysis [28]. In IL-DLPME, the recovery of EDCs was affected by many factors, including the type and volume of the ionic liquid, type and volume of dispersive solvent, pH of the sample solution, extraction time, and centrifugation time, etc. [8, 29-32]. In these reports, the conditions for DLPME attempted to be optimized using the classical method, but the interaction effect between independent variables was not taken into consideration. Consequently, it was difficult to determine the optimal conditions for a complex mixture of compounds from different chemical groups. Indeed, it is necessary to use an experimental design to optimize an analytical method for EDCs.

This study was conducted to develop a reliable IL-DLPME method for the analysis of EDCs. To accomplish this, a number of variables, including the type and volume of ionic liquid, pH, type and volume of extraction and disperser solvents, extraction time, centrifugation time, and salt effect were considered to affect the extraction yields of the IL-DLPME and the interaction between variables, and optimization was performed to evaluate the optimal conditions of IL-DLPME. An experimental Plackett-Burman design with two levels and a central composite design (CCD) were employed to determine the effects of various variables on extraction efficiency simultaneously.

Materials and Methods

Reagents and Standards

1-Hexyl-3-methylimidazolium hexafluorophosphate [C_6MIM][PF_6] (99%) and 1-butyl-3-methylimidazolium tetrafluoroborate [C_4MIM][BF_4](99%) were purchased from Chengjie Chemical Company (Shanghai, China) and used as obtained. Standard solutions of BPA and 4-NP were purchased from J&K Chemical Ltd. (Beijing, China). Guaranteed reagent-grade sodium chloride was obtained from Beijing Chemical Reagent Factory (China). All other reagents were of HPLC grade. Helium gas with a purity of 99.999% was supplied by Deyang Special Gas Co. (Shandong, China). Working solutions were prepared daily by proper dilution of the stock solutions using ultra-pure water. All solutions were stored at 4ºC in the dark until used.

Apparatus

The HPLC system consisted of a quaternary pump (Thermo Fisher Scientific, USA) equipped with a 25 μL loop and a Surveyor PDA detector. A Hypersil BDS C18 column (2.1 mm × 150 mm, 5 μm particle size) was held at 30ºC in a Surveyor column compartment. A 10 μL aliquot of sample was injected with an autosampler using a binary mobile phase composed of 40% water and 60% methanol at a constant flow rate of 0.3 mL/min.

Mass spectrometry was conducted on a Finnigan LCQ DECA MAX multi-ion trap mass spectrometer fitted with an ESI-MS source and controlled by an XCalibur workstation. The ESI source conditions were established to gain an average maximum intensity of the precursor ions. The nitrogen nebulizer pressure was set at 30 arb and the drying temperature of the nitrogen was set at 275ºC with a capillary voltage of 4000 eV. For MS-MS, high purity He was used as the collision gas. To optimize the selective reaction monitoring, direct injection of each individual compound in methanol was used.

Dispersive Liquid Phase Microextraction

A 5 mL water sample spiked with 5 μg/L BPA and 10 μg/L 4-NP was added to a 10 mL glass vial with a conical bottom. Methanol (500 μL) used as disperser solvent with 50 μL [C_6MIM][PF_6] as extraction solvents, which was prepared before use, was rapidly introduced into sample solution. Introduction of the dispersive solvent resulted in the formation of a cloudy mixture, which was then gently shaken and centrifuged for 3 min at 6,000 rpm until the disperser solvent was deposited in the bottom of the vial. The supernatant was removed, and the residue was dissolved in 100 μL methanol, after which 10 μL of this solution was injected for analysis.

Water samples, including tap water and surface water, were collected for validation of the proposed method. Tap water was collected in our laboratory and surface water was obtained from a local river. Water samples were filtered through 0.45 μm micro-pore membranes and stored at low temperature before use.

Experimental Design and Statistical Analysis

The objective of the experimental design was to determine which factors influenced the sensitivity of IL-DLPME. An experimental Plackett-Burman design with two levels and a CCD were used to evaluate the significant factors involved in the extraction. The independent factors, type and volume of ionic liquid, type and volume of disperser solvents, pH, and salt effect were investigated.

The polynomial equation of the response variable with respect to the discrete and continuous factors was regressed using the Design Expert 7.1.0 software package and Minitab 14. A quadratic polynomial regression model was used to predict the response. The model proposed for response Y is expressed as Eq (1):

$$Y = b_0 + \sum b_i X_i + \sum b_{ii} X^2{}_{ii} + \sum b_{ij} X_i X_j \quad (1)$$

...where Y is the response variable, b_0 is a constant, b_i is a linear coefficient, b_{ij} is a cross-product coefficient, b_{ii} is a quadratic coefficient, and X is the coded level of the independent variables.

The fit of the model was evaluated using the coefficients of determination (R^2) and analysis of variance (ANOVA). Three-dimensional response surface curves were constructed to visualize the response.

Results and Discussion

Preliminary Selection of Ionic Liquid

In the IL-DLPME procedure, the efficiency is dependent on the chemical nature of the target analytes. For this method, it is essential to select a proper extraction solvent with good chromatographic behavior and extraction properties. The inexpensive imidazolium ionic liquids, $[C_6MIM][PF_6]$ and $[C_4MIM][BF_4]$, were considered as extraction solvents in the DLPME. Trial results showed that $[C_6MIM][PF_6]$ enabled better enrichment and isolation of BPA and 4-NP from aqueous solution than $[C_4MIM][BF_4]$ because of the high solution in the water of $[C_4MIM][BF_4]$. Therefore, $[C_6MIM][PF_6]$ was selected as the extraction solvent for further experiments.

Effect of Type of Dispersive Solvent

The prerequisite for selection of the dispersive solvent is that it can be miscible with the extraction solvent and aqueous solution [13]. Accordingly, three solvents were selected: acetone, methanol, and acetonitrile. A total of 0.5 mL of each dispersive solvent with $[C_6MIM][PF_6]$ was then applied in the subsequent tests. As shown in Fig. 1, the use of methanol as a dispersive solvent resulted in better enrichment efficiencies of the two compounds than the other solvents. Therefore, methanol was adopted as the dispersive solvent for subsequent tests.

Plackett-Burman Design with Two Levels

During the extraction, the IL-DLPME efficiency depends on numerous factors; therefore, sequential study of all potential factors would be complex and time-consuming. A first-order Plackett-Burman design with two-levels is useful for preliminary studies or the initial steps of an optimization because it makes evaluation of multiple factors relatively simple and economical [33]. Accordingly, a Plackett-Burman experimental design was developed in this study to screen the main factors that could affect extraction efficiency.

Table 1. Independent variables, their levels and symbols and factorial design.

Run No.	A: Volume of extraction solution (μL)	B: Volume of dispersive solvent (μL)	C: pH	D: NaCl concentration (g/mL)
1	1	1	-1	1
2	1	-1	-1	1
3	-1	-1	1	-1
4	-1	1	1	-1
5	-1	1	1	-1
6	1	1	1	1
7	-1	-1	-1	-1
8	1	1	-1	1
9	-1	1	-1	-1
10	1	-1	1	1
11	1	-1	1	1
12	-1	-1	-1	-1
-1	30	200	3	0
1	60	600	11	0.2

Based on preliminary studies and experimental results, the independent variables were set as follows (low/high value): volume of extraction solution (μL) 30/60, volume of dispersive solvent (μL) 200/600, pH 3/11 and NaCl concentration (g/mL) 0/0.2. The factors, their levels, and their coded and uncoded values are shown in Table 1. Owing to uncontrolled systematic errors, the order of the tests was randomized to avoid any skewness in the levels of the measured compounds.

An experimental design with 12 runs was conducted to screen out factors that had the greatest influence on the response of the BAP and 4-NP. The results of ANOVA in the Plackett-Burman design matrix are shown in Table 2.

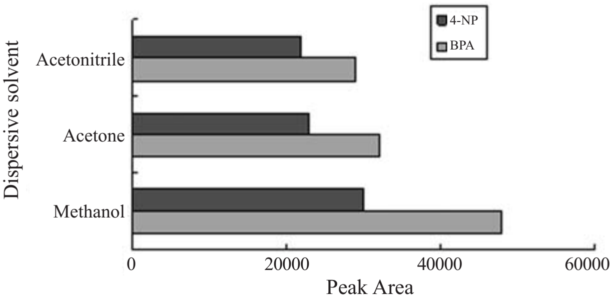

Fig. 1. Effects of different dispersive solvents on the efficiencies of enrichment of BPA and 4-NP.

Table 2. Results of analysis of variance for Plackett-Burman design.

Variables	Sum of Squares	df[a]	Mean of Squares	F Value	Prob.>F
Model	4.438×10^{11}	10	4.438×10^{11}	6.02	0.0305*
A	1.195×10^{11}	1	1.195×10^{11}	25.98	0.0038**
B	9.479×10^{10}	1	9.479×10^{10}	12.86	0.0158*
C	8.457×10^{10}	1	8.457×10^{10}	11.48	0.0195*
D	3.491×10^{10}	1	3.491×10^{10}	4.74	0.0814
AB	3.049×10^{10}	1	3.049×10^{10}	4.14	0.0976
AC	6.592×10^{8}	1	6.592×10^{8}	0.089	0.7769
AD	2.274×10^{9}	1	2.274×10^{9}	0.31	0.6025
BC	7.643×10^{5}	1	7.643×10^{5}	1.037×10^{-4}	0.9923
BD	1.577×10^{9}	1	1.577×10^{9}	0.21	0.6630
CD	3.084×10^{9}	1	3.084×10^{9}	0.42	0.5462
Residual	3.684×10^{10}	5	7.368×10^{9}		
Cor Total	4.807×10^{11}	15			

*significant at the 5% level, **significant at the 1% level, [a]−degrees of freedom.

Table 3. Three selected factors and their three levels.

Variable	Variable levels				
	-α(-1.68)	-1	0	1	+α(+1.68)
A: Volume of extraction solution (μL)	19.8	30	45	60	70.2
B: Volume of dispersive solvent (μL)	64	200	400	600	736
C: pH	0.28	3	7	11	13.72

F-test values less than 0.050 indicate that the response variable is significantly affected by the independent variable. In such cases, the volume of the extraction solution (A), volume of the dispersive solvent (B), and pH (C) are significant parameters. Conversely, values greater than 0.050 indicate that the variable is not significant, which was the case for NaCl in this study. However, although the independence of salt-out effect is not significant, the addition of NaCl with agitation, which only enhanced the extraction efficiency of IL-DLPME, made the procedure more effective by allowing the transference of analytes from matrix to the extraction solvent [34]. Thus, 0.1 g/mL NaCl (on average) was used in the following experiments.

Central Composite Design

Factorial designs are primarily used to screen out significant factors, but also can be used to model and refine a process [35]. In this study, a three-factor three-level CCD is required to locate an optimum set of experimental conditions. The total number of experiments needed (*N*) for the CCD is determined by Equation (2):

$$N = 2^f + 2f + N_0 \tag{2}$$

...where f is the number of variables and N_0 is the number of central points. Therefore, 20 experiments need to be run for a CCD with eight (2^3) factorial points, six central points (star points) and six replicates of the central points, which are used to estimate the experimental error (pure error). The coded value ±1 indicates the distance from the center of the design space to a factorial point, with the $\pm\alpha$ ($|\alpha| > 1$) value being the mean of the distance from the center of the design space to the star point. The value of α was set to 1.68 based on the criterion of optimality, which can cause these points to be the same distance to the center. The experiments were run in a random order to ensure that variability is observed in the response.

To ensure the nonlinearity of the MS response, a quadratic model was employed to build an RSM for estimation of the response curvature in the CCD. The volume of extraction solution (A), volume of dispersive solvent (B), and pH (C) were used to determine the significance, but the NaCl concentration was not considered.

Table 4. Experiments performed in the central composite design.

Run No.	A: Volume of extraction solution (μL)	B: Volume of dispersive solvent (μL)	C: pH
1	-1	-1	-1
2	-1	1	1
3	0	0	0
4	0	0	0
5	1	1	-1
6	0	0	0
7	-1	1	-1
8	1	1	1
9	1	-1	1
10	0	0	0
11	-1	-1	1
12	1	-1	-1
13	1.68	0	0
14	-1.68	0	0
15	0	0	0
16	0	0	-1.68
17	0	0	1.68
18	0	1.68	0
19	0	0	0
20	0	-1.68	0

In the CCD method, a minimum or low level (denoted as -1), a central or medium level (denoted as 0), and a high or maximum level (denoted as 1) are defined for each experimental factor (Table 3). The factor levels and the design matrix are shown in Table 4, and the ANOVA and the model terms are shown in Tables 5 and 6. The results showed that the linear terms of A, C, and the cross-product A×B, A×C had a significant effect on the response (MS response).

The quality of fit of the polynomial model equation is expressed by the coefficient of determination (R^2 and adjusted-R^2 shown in Table 5). R^2 is a measure of the amount of variation around the mean that is explained by the model. The adjusted-R^2 is adjusted for the number of terms in the model [35]. The values representing the accuracy and general reliability in the polynomial model were adequate.

A second-order polynomial equation was used to express the MS response as a function of the independent variables as follows (using coded factors):

$$\begin{aligned} Y = 1443502 - 28134\,A - 185\,B - 26534\,C + 31AB + \\ + 727\,AC - 0.69BC - 85A^2 - 0.81B^2 - 98C^2 \end{aligned} \tag{3}$$

The regression equation (Eq. 3), which has three main effects, three two-factor interaction effects, and three curvature effects with the estimated coefficient, can be employed to predict the optimization of the response *Y* within the range of variables in the experiment. A variable is assumed to have a greater effect on the response if its coefficient is relatively larger than the others. Variables with a positive coefficient enhance the effect toward the response, while those with a negative coefficient have the opposite effect. As can be inferred from Eq. 3, which includes the coefficient for each effect, the volume of extraction solvent (A, -28314) and pH (C, -26534) had negative coefficients.

A normal probability plot of the residuals (Fig. 2) reveals a nearly linear distribution, which indicates that errors are evenly distributed and supports a least-square fit.

Interactions between two different factors can be interpreted from the interaction diagrams (Fig. 3). Areas in which the two lines are not parallel indicate that the effect of one factor depends on the level of the other factor. Interactions were observed between the volume of extraction solution

Table 5. Analysis of variance (ANOVA) for fitted quadratic model.

Regression	DF	Sum of Squares	R-Square	F Value	Prob. >F
Model	9	3.0348×10^{11}	3.372×10^{10}	7.54	0.002**
Linear	3	9.9978×10^{10}	2.818×10^{10}	6.30	0.011*
Quadratic	3	1.150×10^{10}	8.090×10^{9}	1.81	0.209
Cross-product	3	1.920×10^{11}	6.400×10^{10}	14.32	0.001**
Lack of Fit	5	2.072×10^{10}	4.144×10^{10}	0.86	0.562
Pure Error	5	2.398×10^{10}	4.796×10^{10}		
Total	19	3.481×10^{11}			
R^2=87.16%		Ajust-R^2=75.61%			

*significant at the 5% level, **significant at the 1% level

Table 6. Results of regression analysis of a full second-order polynomial model

Variable	DF	Standard Error	T Value	P
intercept	1	27163.85	4.794	0.001**
A	1	19670.53	-3.218	0.009**
B	1	18232.21	-0.346	0.736
C	1	18566.54	-3.621	0.005**
A×B	1	27043.33	3.407	0.007**
A×C	1	27043.33	6.051	0.000**
B×C	1	24688.61	-0.084	0.935
A2	1	17938.97	-1.071	0.309
B2	1	16142.72	-2.012	0.072
C2	1	17803.55	-1.245	0.242

**significant at the 1% level.

and volume of dispersive solvent (Fig. 3a), and between the volume of extraction solution and pH (Fig. 3b), but not between the volume of dispersive solvent and pH (Fig. 3c).

To express the interaction effects on the response in a better way, three-dimensional response surface curves were created as a function of the interaction of any two of the variables by holding the other variable at its central level (0) (Figs. 4-6). The plot shape allows estimation of the significance of the mutual interactions between independent variables. These plots are a visual representation of the relationship between the response and each experimental factor.

The response surface curve of the predicted response as a function of volume of extraction solvent and volume of dispersive solvent (Fig. 4) shows that the response has a good relationship with the change in the volume of extraction solvent and volume of dispersive solvent. Initially, as the volume of extraction solvent increases from 30 to 40 µL,

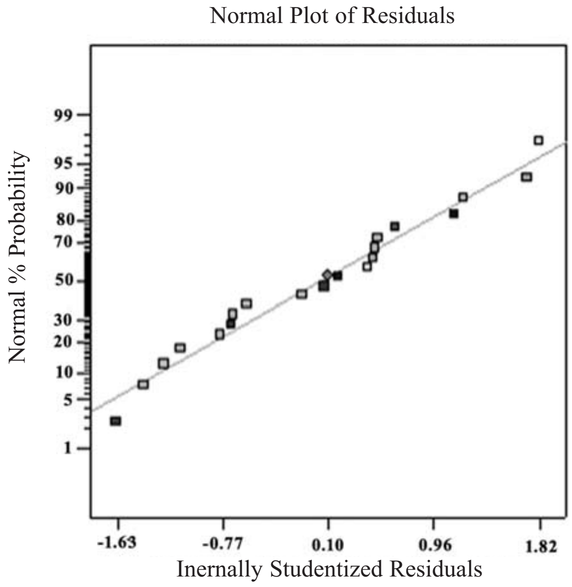

Fig. 2. Normal probability plot of residuals for the response.

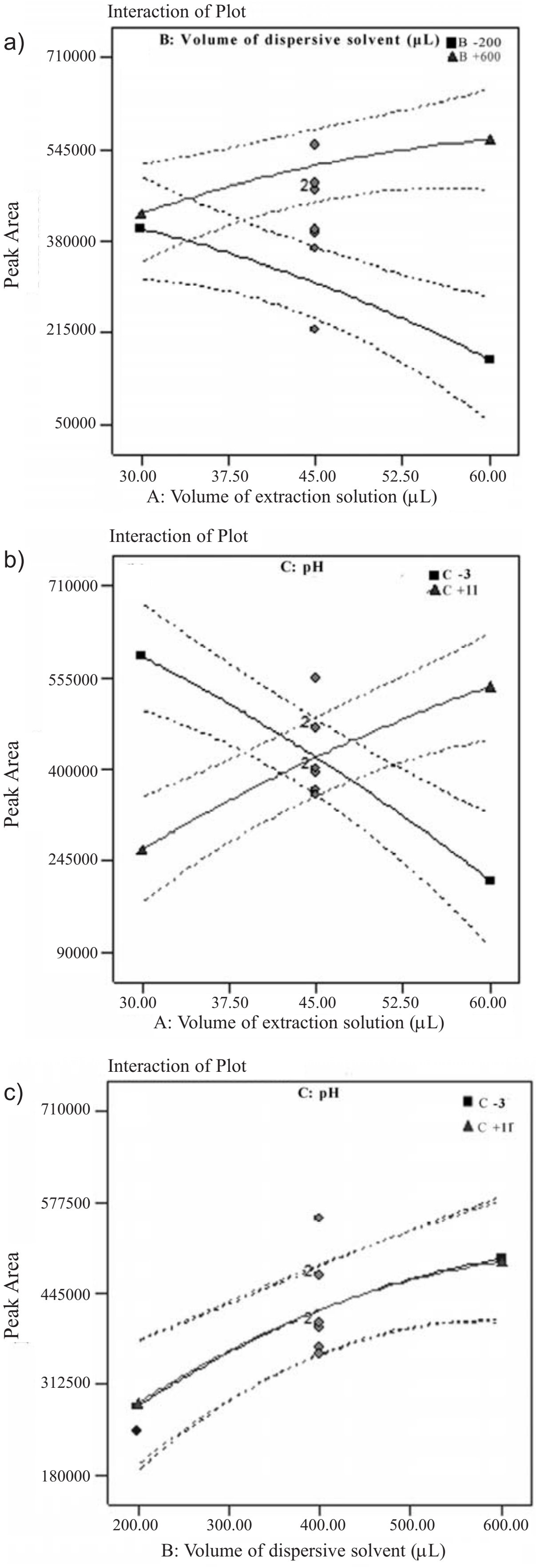

Fig. 3. Two-factor interaction and their effects on efficiency: (a) volume of extraction solvent and volume of dispersive solvent, (b) volume of extraction solvent and pH, and (c) volume of dispersive solvent and pH.

the change in response is very low, indicating that most of the targets were enriched. However, as the volume of the extraction solvent increases further to 60 μL, the response decreases greatly (Fig. 4). This presumably occurred because when the volume of extraction solvent was between 30 μL and 40 μL, the cloudy solution in the aqueous sample formed very well and the surface area between the ionic liquid and aqueous phase was infinitely large. The increase in the volume of extraction solvent provided a large opportunity for the extraction droplets to combine to form a larger droplet, which decreases the surface area between ionic liquid and the aqueous phase, and increases the solubility of BPA and 4-NP in the water. *Y* increases as the volume of dispersive solvent increases. However, when the volume of dispersive solvent reaches 500 μL, the response remains stable. These findings indicate that at a low volume of dispersive solvent, the cloudy state is not formed well, resulting in low extraction yields. Accordingly, higher volumes of dispersive solvent enable equilibrium to be achieved.

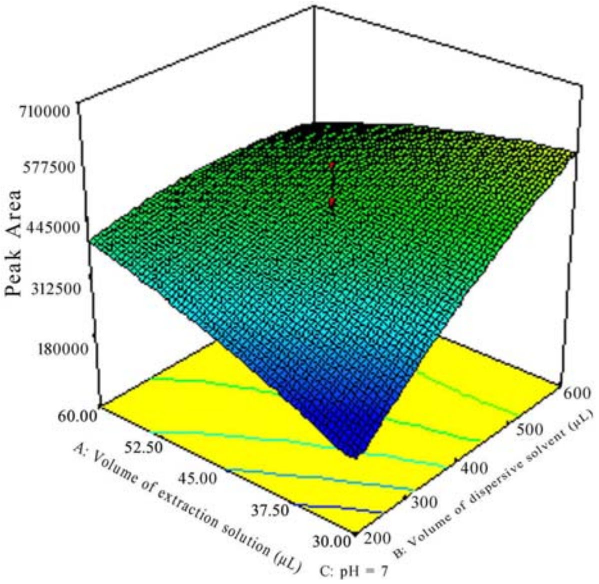

Fig. 4. Response surface curve showing the predicted response as an interaction function of volume of extraction solvent ranging from 30 to 60 μL and volume of dispersive solvent ranging from 200 to 600 μL by holding pH at its central level (7).

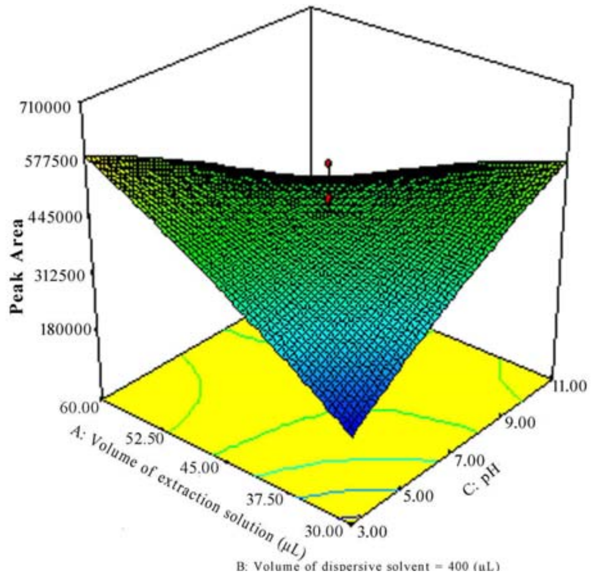

Fig. 5. Response surface curve showing the predicted response as an interaction function of volume of extraction solvent ranging from 30 to 60 μL, and pH ranging from 3 to 11 by holding the volume of dispersive solvent at its central level (400 μL).

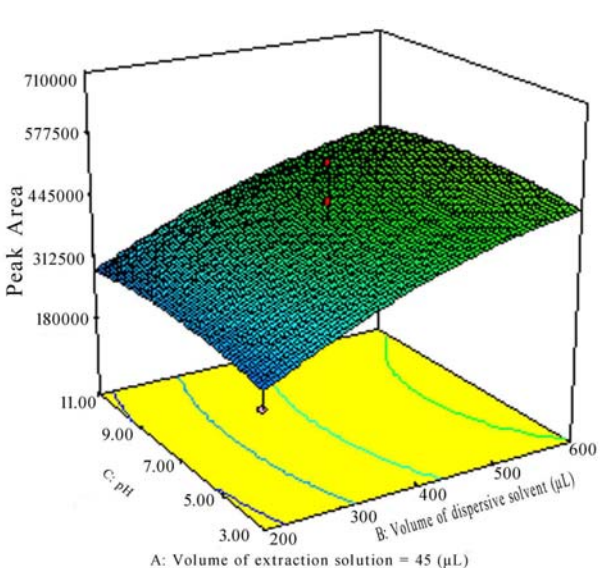

Fig. 6. Response surface curve showing the predicted response as an interaction function of the volume of dispersive solvent ranging from 200 to 600 μL and pH ranging from 3 to 11 by holding the volume of extraction solvent at its central level (45 μL).

As shown in Fig. 5, as pH increases the enrichment factor increases. The negative effect of the volume of the extraction solvent on the response caused a saddle formed by the interaction of the volume of extraction solvent and pH. This may have occurred because the change in the pH of the solution results in the protonation and deprotonation of BPA and 4-NP; thus, their solubilities in water are enhanced significantly and the amount of targets in the sedimented ionic liquid phase is reduced.

The response surface curve showing the predicted response as a function of the volume of dispersive solvent and pH is shown in Fig. 6. Accordingly, in subsequent experiments, 30 μL of extraction solvent, 500 μL of dispersive solvent, and pH 7 are sufficient for the extraction.

These adjusted optimum conditions were applied in the following experiments. The experiments confirm the validity of the predicted model; therefore, the model was considered to be accurate and reliable.

Evaluation of the Method Performance

Optimum conditions were used to obtain analytical characteristics for the proposed IL-DLPME method (Table 7). The results revealed that the linearity of the calibration

Table 7. Quantitative results for IL-DLPME analysis of BPA and 4-NP using the adjusted optimized conditions from the RSM.

Compound	Linear Range (μg/L)	R^2	RSD (%) (n=6)	LOD (μg/L)
BPA	1-70	0.9980	8.4	0.76
4-NP	0.5-24	0.9976	9.3	0.055

Table 8. Determination of BPA and 4-NP in tap water and surface water using optimized IL-DLPME.

Compound	Tap water		Surface water	
	Found (μg/L)	Recovery (%)	Found (μg/L)	Recovery (%)
BPA	ND	78.6	0.2	90.3
4-NP	ND	80.3	ND	93.5

ND – Not detected

ranged from 1 to 70 μg/L for BPA and from 0.5 to 24 μg/L for 4-NP. The coefficients of determination (R^2) ranged from 0.9976 to 0.9980. The reproducibility was investigated in six replicate experiments using an aqueous standard solution with 2 μg/L targets. The relative standard deviations ranged from 8.4 to 9.3%. The limits of detection based on a signal-to-noise ratio of three ranged from 0.055 to 0.76 μg/L. These results indicated that the method was a reliable and simple green procedure for determining BPA and 4-NP at trace levels.

Analysis of Real Water Samples

Two real environmental water samples (tap water and surface water obtained locally) were used to investigate the applicability of the proposed method. As shown in Table 8, tap water was free of BPA and 4-NP contamination, while BPA was detected at 0.2 μg/L level in the surface water. The recoveries for BPA and 4-NP ranged from 78.6% to 93.5% in tap water and surface water (Table 8), which demonstrates that these matrices have little effect on IL-DLPME.

Conclusions

In this study, the extraction of BPA and 4-NP from drinking water for analysis by IL-DLPME coupled to high-performance liquid phase chromatography mass spectrometry was optimized. A second-order RSM was used to optimize the independent variables for extraction yields of BPA and 4-NP. The volume of extraction solvent, volume of dispersive solvent, and pH were important variables. ANOVA of CCD was used to reveal quadratic and interaction terms. The results showed a detailed effect of factors on each other and on efficiency. These statistical experiments allowed determination of the optimum experimental conditions for the factors that had the greatest effect on the response, and used a minimum number of trials. This optimized extraction with IL-DLPME is a useful tool for the analysis of BPA and 4-NP in water samples.

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